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National Institute of General Medical Sciences

PHARMACOLOGY RESEARCH ASSOCIATE PROGRAM OF THE NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES NATIONAL INSTITUTES OF HEALTH

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PHARMACOLOGY RESEARCH ASSOCIATE PROGRAM

OF THE

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

NATIONAL INSTITUTES OF HEALTH

CHRISTINE K. CARRICO, PH.D., PROGRAM DIRECTOR

RUTH A. LINN, PROGRAM ASSISTANT

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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INTRODUCTION

In 1959 the National Institutes of Health (NIH) initiated the Associate Training Programs in the Medical and Biological Sciences—now called the Medical Staff Fellowship Program—to train individuals for careers in biomedical research.

The National Institute of General Medical Sciences (NIGMS) established the Pharmacology Research Associate component of the NIH program in 1965. Unlike the rest of the NIH program, which is open only to those holding professional degrees such as an M.D., D.D.S., or D.V.M., individuals with a Ph.D. degree in pharmacology or a related science are eligible to be Pharmacology Research Associates.

The goal of the NIGMS program is to develop leaders in pharmacological research for key positions in academic, industrial, and Federal research laboratories. It is intended for those who have made a commitment to the pharmacological sciences in their training or research, and for those with backgrounds in clinical medicine or basic science who wish to acquire specialized experience in the field of pharmacology.

EXPERIENCE OFFERED

Pharmacology Research Associates receive 2 years of postdoctoral training in one of the laboratories of the National Institutes of Health and the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA).

Professional growth is stimulated through personal guidance by outstanding senior scientists, chosen by mutual agreement between the scientist and the associate. A variety of laboratory problems and different research approaches advance both the work in progress and the competence of the prospective independent investigator. During their tenure, the associates devote most of their time to laboratory research in the biomedical sciences. They have no formal clinical responsibilities.

PROGRAM AREAS

The choice of a specific laboratory depends upon the candidate's previous training and career plans. Those who have already received adequate graduate training or conducted meritorious research in pharmacology may request any senior NIH or ADAMHA scientist as a preceptor. Since the objective of this program is to offer postdoctoral training opportunities to those interested in pursuing a research career in pharmacology, applicants without training or experience in pharmacology should select program areas which will provide such opportunities. All applicants are encouraged to give these program areas primary consideration. The Pharmacology Research Associate Advisory Committee offers counseling to applicants invited to the NIH for interviews.

Descriptions of the laboratories that currently provide training opportunities in the pharmacological sciences begin on page 3.

CLINICAL PHARMACOLOGY OPTION

Clinical pharmacology is an evolving research discipline that addresses the need for investigators to carry out pharmacological studies that relate to the mechanism(s) of action of clinically relevant drugs. An opportunity is available for 2 years of research training specifically in an area of clinical pharmacology. Applicants for this training should have the M.D. degree and a *minimum* of 1 year, preferably 2, of graduate medical education (internship or residency). This is a particularly good opportunity for M.D.'s who have not had extensive independent laboratory experience but who are committed to obtaining such experience. For this reason, intensive laboratory research in at least one of the programs described in the next section constitutes 50 to 75 percent of the clinical pharmacology program. In order to prepare associates either to relate laboratory methods to studies in humans or to carry out mechanistically oriented studies in humans, the program also includes training in such general clinical pharmacological principles as pharmacokinetics, pharmacodynamics, biostatistics, and drug evaluation.

In addition to the listed laboratory preceptors, investigators who are actively engaged in clinical pharmacological research in the Warren Grant Magnuson Clinical Center, NIH, are available to address associates' special areas of need on an individualized basis. These preceptors include but are not limited to:

James R. Gillette, Ph.D., Chief, Laboratory of Chemical Pharmacology, National Heart, Lung, and Blood Institute

Harry Keiser, M.D., Clinical Director, National Heart, Lung, and Blood Institute

Charles Myers, M.D., Chief, Clinical Pharmacology Branch, National Cancer Institute

Daniel W. Nebert, M.D., Chief, Laboratory of Developmental Pharmacology, National Institute of Child Health and Human Development

Snorri S. Thorgeirsson, M.D., Ph.D., Chief, Laboratory of Experimental Carcinogenesis, National Cancer Institute

Markku Linnoila, M.D., Ph.D., Chief, Laboratory of Clinical Studies, National Institute on Alcohol Abuse and Alcoholism

William Z. Potter, M.D., Ph.D., intramural clinical pharmacologist, serves as coordinator of each associate's overall training in clinical pharmacology. The Clinical Pharmacology Associates' research experiences are planned individually to meet the needs dictated by previous training, experience, and career goals. This research experience can involve both laboratory and human investigation.

A training plan, including formal coursework, is developed for each associate. A series of seminars are organized with the participation of the Clinical Pharmacology Associates to ensure that their needs are met.

Candidates who are interested in the clinical pharmacology option under the Pharmacology Research Associate Program should so indicate in a covering letter submitted with their applications. An applicant may be considered for both the regular Pharmacology Research Associate Program and the clinical pharmacology option.

SEMINARS AND EVENING COURSES

Associates participate in formal tutorial seminars and informal discussion groups which provide an opportunity for them to master selected topics not adequately covered during their academic training. Lectures by prominent scientists are also scheduled. In addition, trainees may take courses in such areas as applied mathematics, experimental statistics, medicinal chemistry, human biochemical genetics, molecular biophysics, and instrumentation.

Graduate-level evening courses are offered on the NIH campus by the Foundation for Advanced Education in the Sciences, Inc. Founded by scientists who subscribe to the view that learning, research, and teaching are mutually reinforcing processes essential to the evolution of science, this independent organization offers unique and convenient opportunities for academically creditable instruction.

APPOINTMENTS

NIGMS has 11 positions available for Pharmacology Research Associates beginning July 1 of each year. Pharmacology Research Associates are appointed as staff fellows or medical staff fellows. Candidates must be U.S. citizens or permanent residents of the United States who have been awarded a doctoral degree, or who have been certified by a university as meeting all the requirements leading to a doctorate. The degree must be in a biomedical or related science and must have been received within the 5 years preceding the date of application.

The stipend is determined by the candidate's educational and professional experience and is comparable to Civil Service salary at a similar level. Associates who perform well and are recommended by their preceptors are eligible for a stipend increase after 1 year.

Allowances are available to cover the cost of travel to Bethesda, Maryland, from the appointee's place of residence. Payment of charges for shipping personal goods will only be provided for medical staff fellows.

Associates earn 4 hours of annual and 4 hours of sick leave every 2 weeks. A number of health insurance plans are available; costs are shared by the associate and the Federal Government. A group life insurance program is also offered to those who wish to participate, with premiums deducted from the associate's stipend.

APPLICATION

Additional information and application forms may be obtained by writing to:

Pharmacology Research Associate Program
National Institute of General Medical Sciences
National Institutes of Health
Westwood Building, Room 919
Bethesda, Maryland 20892
(301) 496-7707

Applications must be received by November 17, 1986, for appointments beginning July 1, 1988. Early applications for 1989 will also be accepted. The applicant is also responsible for requesting that the following materials be sent to the above address by November 17, 1986, to complete the application:

- One *official* copy of academic transcripts from graduate and undergraduate schools sent directly from the institution.
- Professional references from three separate sources on evaluation forms which are included in the application kit.

SELECTION

Each candidate's qualifications are carefully reviewed by the Pharmacology Research Associate Committee. Selection is made on a highly competitive basis, with preference given to applicants with outstanding academic records and references. Other considerations include intellectual attainment, demonstrated research interest, and research accomplishments.

Candidates should be prepared to come to the NIH for interviews *at their own expense* during a 2-week interview period in January 1987. All interviews are *by invitation only*. Following the interviews, applicants will be asked to indicate their preferences for a preceptor, which will be coordinated with the preceptors' preferences among the applicants interviewed. Successful candidates will be notified and given an opportunity to accept or reject the position for which they were selected.

DISCRIMINATION PROHIBITED

Under provisions of applicable public laws enacted by Congress since 1964, no person in the United States shall, on the grounds of race, color, national origin, handicap, or age, be excluded from participation in, be denied the benefits of, or be subjected to discrimination under any program or activity (or, on the basis of sex, with respect to any education program or activity) receiving Federal financial assistance. In addition, Executive Order 11141 prohibits discrimination on the basis of age by contractors and subcontractors in the performance of Federal contracts, and Executive Order 11246 states that no federally funded contractor may discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin. Therefore, the programs of the National Institute of General Medical Sciences must be operated in compliance with these laws and Executive Orders.

LABORATORIES AND PRECEPTORS PROVIDING TRAINING IN THE PHARMACOLOGICAL SCIENCES

NATIONAL CANCER INSTITUTE

Laboratory of Molecular Biology
Ira Pastan, M.D.

The Molecular Biology Section of the Laboratory of Molecular Biology is interested in developing immunotoxins for the treatment of human cancer. To accomplish this, *Pseudomonas* exotoxin is coupled to monoclonal antibodies that react with specific human cancers. The activity of these conjugates is assessed in cell culture and in animal models. Toxicity studies are currently being carried out in monkeys with the first promising immunotoxins in preparation for clinical testing. The mechanisms by which immunotoxins enter and kill cells is studied by biochemical, genetic, and cell biological approaches in order to devise ways to improve the therapeutic efficiency of these agents.

Laboratory of Molecular Biology
Molecular Cell Genetics Section
Michael M. Gottesman, M.D.

This section develops tissue culture genetic models for the analysis of the mechanism(s) of drug resistance in human cancer cells. The scientists' work has emphasized the establishment of human cell lines resistant to multiple drugs with the aim of understanding the molecular basis of this resistance. Genetic studies include dominance analysis using somatic cell hybrids and techniques of DNA-mediated gene transfer to clone mutant or amplified genes involved in the multiple-drug-resistance phenotype. Biochemical studies include use of monoclonal antibodies to study cell-surface alterations in resistant cells and studies on uptake of drugs by resistant cells. Other research focuses on resistance of cell lines to antimicrotubule agents due to alterations in α- and β-tubulins and the role of cyclic AMP in regulating cell growth.

Laboratory of Mathematical Biology
Pharmacology of Biologicals Program
John N. Weinstein, M.D., Ph.D.

The principal aim of this group is to understand the pharmacology of biologic agents. As it becomes increasingly feasible to tailor biologicals to order, the lack of information on their pharmacology remains a major barrier to rational design. The group is taking a combined experimental/theoretical approach to the question, with current emphasis on monoclonal antibodies. Experiments are being done at several levels, ranging from detailed analyses of antibody binding and cell biology to whole-animal biodistribution studies. Also included is a program on immunotoxins and other effectors aimed at tumor cell killing and immune modulation. All of the *in vitro* and animal studies are closely correlated with clinical protocols on which members of the group are working.

On the theoretical side, the group is constructing both compartmental and distributed models using data from animal and human studies. Concepts arising from the models are then used to refine or redesign the protocols and also the biologic agents themselves. A current focus is on the delivery of antibodies via lymphatic vessels (rather than the bloodstream) for the diagnosis and therapy of lymphoma and metastatic solid tumors in lymph nodes.

Metabolism Branch
Endocrinology Section
James M. Phang, M.D.

This research program emphasizes the functions of metabolic intermediates as regulatory molecules and the modulation of these functions by hormones. Of special interest is pyrroline-5-carboxylate, the obligate intermediate in the interconversions of proline, ornithine, and glutamate. This molecule serves as a metabolic interlink between amino acids and ribonucleotides and participates in the early cellular events accompanying mitogenic activation by growth factors. Pyrroline-5-carboxylate also acts as an intercellular communicator. It is found in biologic fluids such as plasma and aqueous humor and functions to transfer metabolic signals between cells and tissues.

Several approaches are used to elucidate the mechanisms of the pyrroline-5-carboxylate metabolic interlink and to demonstrate its physiologic significance. These include cellular physiology, biochemistry, molecular biology, and human physiology. This group is studying the processing of these signals to regulate ribonucleotide metabolism and gene expression. The investigators are also characterizing the enzymes of this regulatory system and planning to clone the genes coding for these enzymes. With the understanding of these mechanisms in normal and malignant cells, the scientists will seek specific pharmacological approaches in order to manipulate pyrroline-5-carboxylate-mediated cellular response in normal and neoplastic cells.

Laboratory of Tumor Virus Biology
Peter M. Howley, M.D.

This laboratory engages in several areas of research to determine critical cellular and molecular factors involved in virus-associated transformation. Studies are designed to: (1) identify and characterize exogenous viruses associated with the initiation or progression of neoplasia in humans or in animals as models for human neoplasia; (2) elucidate the mechanisms by which viruses associated with naturally occurring carcinomas may induce or initiate neoplasia; (3) characterize and define the biology and molecular biology of viruses associated with naturally occurring carcinomas; (4) identify and characterize factors involved in viral and cellular gene regulation pertinent to carcinogenesis; and (5) elucidate and define the cellular and molecular basis of transformation and carcinogenic progression.

The major research effort of the laboratory is focused on the molecular biology of the papillomaviruses, including transcriptional regulation, transformation, plasmid replication, and carcinogenesis. The laboratory has also been involved in developing the papillomaviruses as mammalian cell cloning vectors and is interested in using these vectors to study regulated genes such as the human β-interferon gene and the rat pre-proinsulin gene. These studies are designed to determine the genetic sequences involved in proper gene regulation and to isolate cellular protein factors required for this regulation.

Laboratory of Cellular Carcinogenesis and Tumor Promotion
Molecular Mechanisms of Tumor Promotion Section
Peter M. Blumberg, Ph.D.

Tumor promoters are agents which, although not themselves carcinogenic, induce tumors in animals previously exposed to a sub-effective dose of a

carcinogen. This section is studying the mechanism of action of the most potent class of tumor promoters for mouse skin, the phorbol esters, and has demonstrated that cells and tissues contain specific phorbol ester receptors. Characterization indicates that the major class of these receptors is identical to protein kinase C, to which the phorbol esters bind at a modulatory site. Diacylglycerol, an activator of protein kinase C, appears to be the endogenous analog of the phorbol esters, and the postulated normal role for the phorbol ester receptor/protein kinase C is to mediate responses to that large class of hormones and cellular effectors whose action is associated with phosphatidylinositol turnover rather than elevated cyclic AMP levels. Current research directions include clarifying the interactions of the receptor with membranes, determining the basis of receptor subclasses, defining the mechanism of coupling between phorbol ester binding and kinase activation, and tracing the pathways between substrate phosphorylation and subsequent biologic response.

Laboratory of Experimental Carcinogenesis
Snorri S. Thorgeirsson, M.D., Ph.D.

This laboratory plans, develops, and implements a research program to elucidate mechanisms of malignant transformation in human and animal cells by chemical carcinogens and other cancer-causing agents; determines critical cellular and genetic factors involved in the initiation, promotion, and progression of these transformed cells; and, whenever possible, applies the knowledge obtained from these studies toward the effective prevention of cancer in humans. Studies are designed to: (1) identify and characterize exogenous and endogenous factors controlling the initiation, promotion, and progression of chemically induced tumors; (2) elucidate the mechanisms underlying the regulation of gene expression and differentiation in both human and animal neoplasia; (3) define the mechanism by which modifiers of cellular differentiation may inhibit and/or promote the neoplastic process; and (4) characterize the metabolic processing and mutagenic potential of both known and suspected carcinogenic aromatic amines.

Laboratory of Experimental Carcinogenesis
Hormone Action and Oncogenesis Section
Gordon L. Hager, Ph.D.

This laboratory's central program concerns the mechanism of gene regulation in eukaryotic cells, particularly with regard to steroid hormone modulation of gene activity. The researchers utilize the mouse mammary tumor virus (MMTV) system, which is responsive to glucocorticoid regulation. This model promoter has been mobilized on high-copy, stable, episomal vectors in cultured cells to permit a detailed analysis of hormone action at the chromatin level.

The laboratory is also involved in the development of vectors for the efficient transmission of genes under expression control, both for basic investigations and in medical applications. These vectors are retrovirus-based and utilize hormone-regulated promoters to permit control of expression after gene transmission. It is expected that control of gene activity will become a central issue in gene therapy protocols.

Finally, the group is interested in mechanisms of oncogenesis, specifically in the function of the *ras* oncogene and in the mechanisms of MMTV-induced mammary cancer.

Laboratory of Human Carcinogenesis
Curtis C. Harris, M.D.

The Laboratory of Human Carcinogenesis conducts investigations to assess: (1) mechanisms of carcinogenesis in epithelial cells from humans and experimental animals, (2) experimental approaches in biological systems for the extrapolation of carcinogenesis data and mechanisms from experimental animals to the human situation, and (3) host factors that determine differences in carcinogenic susceptibility among individuals.

The three major areas of investigation are: *Molecular and Biochemical Epidemiology* focuses on measurement of gene polymorphism by molecular approaches (e.g., DNA polymorphism) to identify host susceptibility factors that predispose to cancer; measurement of carcinogen-DNA adducts and other carcinogen-induced lesions in biological samples from individuals in environments associated with high and low risk for cancer; and studies of interactions between the effects of cocarcinogens and carcinogens. *Carcinogen Macromolecular Interaction* involves studies of the activation of cellular oncogenes by carcinogens; identification of metabolic pathways of carcinogen activation and deactivation; inter- and intragenic damage and rearrangements caused by chemical and physical carcinogens; and determination of the importance of repair of carcinogen-induced damage to DNA and chromosomes in carcinogenesis. *In Vitro*

Carcinogenesis investigates the mechanisms of neoplastic transformation; the role of oncogenes in human cell carcinogenesis; phenotypic and genetic alterations during *in vitro* carcinogenesis; the relationship between carcinogenesis, mutagenesis, and differentiation in mammalian cells; and extra-, inter-, and intracellular factors modulating growth and differentiation of human epithelial cells.

Laboratory of Pharmacology and Experimental Therapeutics
David G. Johns, M.D., Ph.D.

The Laboratory of Pharmacology and Experimental Therapeutics is made up of three sections: Medicinal Chemistry, Molecular Toxicology, and Biochemical Pharmacology. The laboratory conducts an integrated program for the rational discovery of antitumor agents, implements basic research on mechanisms of antitumor drug action and drug toxicity, incorporates knowledge of biochemical and molecular mechanisms into a drug synthesis program aimed at optimizing drug efficacy through enhancement of antitumor activity/selectivity and/or minimization of toxicity, and develops strategies for improving the clinical utility of new or existing anticancer drugs by overcoming tumor resistance and/or by protection of normal tissues against toxicity. Compounds with potential antitumor activity are synthesized, and effects of such agents are assessed in experimental tumor systems *in vitro* and *in vivo* and on a variety of potential subcellular target sites (e.g., nucleic acids, nuclear proteins, microtubular protein, and enzyme systems). Analytical methodology is developed for *in vivo* studies with new agents and, where warranted, biologic studies with these agents are extended to the preclinical and Phase I stages. At the present time, three agents synthesized and developed within the laboratory are in Phase I or II clinical trials, while a fourth agent is scheduled for a clinical trial within the next year. Other agents are under active study. A wide range of methodologies are currently in use, including soft agar cloning and other tissue culture techniques; instrumental analysis, with emphasis on mass spectrometry, electron microscopy, high pressure liquid chromatography, and affinity chromatography; DNA and RNA isolation and characterization; hybridization; autoradiography; pharmacokinetic analysis; and enzyme purification.

Laboratory of Pharmacology and Experimental Therapeutics
Michael R. Boyd, M.D., Ph.D.

The research programs of this laboratory are interdisciplinary in nature and fall into two major areas. One area is analytical and clinical pharmacology, involving studies on qualitative and quantitative aspects of the metabolism and disposition of cancer chemotherapeutic agents using experimental systems, as well as in a clinical setting. Problems are selected for their relevance to the development and/or evaluation of new chemotherapy protocols, and frequently are pursued in collaboration with other National Cancer Institute laboratories. The other major research area concerns the elucidation of fundamental chemicobiologic interactions underlying chemically induced cytotoxicity and carcinogenicity to specific target organs and target cells. Of particular interest is the role that the drug-metabolizing enzymes play in the pathogenesis of extrahepatic target tissue toxicities, especially those involving the lungs or the kidneys. Investigations of hepatic and extrahepatic metabolic "activation" and "deactivation" systems are of interest, as are investigations of the biochemical, physiologic, and morphologic consequences of the *in situ* generation of alkylating metabolites in both normal and neoplastic extrahepatic target cells. These studies are intended not only to characterize mechanisms of chemically induced cancer or cell necrosis, but also to provide a basis for the design of new anticancer drugs with optimal tumoricidal activity but minimal toxicity to normal tissues.

Laboratory of Biological Chemistry
Richard L. Cysyk, Ph.D.

This laboratory brings together scientists who identify, as targets for drug design, cellular reactions that are critical to tumor cell survival and to the control of cell division and differentiation. Emphasis is placed on targets uncovered by recent advances in cell biology. Compounds are designed to interfere with these targets and are evaluated for biochemical and antitumor effectiveness. Pharmacological information—plasma levels, tissue levels, mechanisms of action, transport, and metabolism—is used for experimental chemotherapy and for preclinical evaluation of an agent. An important aspect of the selective toxicity of an agent is the effect of endogenous factors present *in vivo* that can modify the cytotoxic properties of the agent and thereby influence differential

toxicity. This laboratory identifies and quantitates such endogenous factors, when possible, and devises methods to manipulate them to enhance the chemotherapeutic effectiveness of cytotoxic compounds.

Laboratory of Biological Chemistry
Robert I. Glazer, Ph.D.

This laboratory conducts molecular studies of the mechanism of action of differentiating agents and anticancer drugs in human tumor cell lines in tissue culture. Areas currently receiving the greatest emphasis include cellular oncogene and protein kinase expression during cellular differentiation, as well as drug resistance. Current investigations include the effects of immune interferon, tumor necrosis factor, phorbol esters, and other differentiating agents on the induction and characterization of tyrosine and calcium-phospholipid protein kinase activities in HL-60 cells. The latter activities are also being characterized in human tumor lines showing pleiotropic drug resistance. A variety of immunologic and molecular techniques are employed in investigating the various facets of this problem.

Medicine Branch
Medical Breast Cancer Section
Marc E. Lippman, M.D.

The research program of this section deals with the mechanism of action of sex steroid hormones in human breast cancer. This problem has been approached from several directions. A variety of estrogen-regulated genes have been identified and cloned, and the basis of their control by estrogens and antiestrogens is being examined. A large number of hormone- and drug-independent mutants have been derived from wild-type cells and the molecular basis of hormone independence has been explored using biochemical and genetic approaches. Intracellular pathways of growth regulation of human breast cancer have also been explored by the introduction of exogenous genetic material in the form of oncogenes into human breast cancer cells and a delineation of their impact on growth control has been examined. In addition, the cell biology and molecular pharmacology of a variety of tagged monoclonal antibodies and novel estrogens are being explored as imaging agents and as cytotoxic therapeutic tools in cell culture, nude mice, and eventually in clinical studies.

Clinical Pharmacology Branch
Charles Myers, M.D.

This laboratory is involved in the biochemistry of adriamycin-iron complexes, including their free radical products. This process involves examination of how these complexes bind to and cleave DNA. In addition, studies are planned to assess the biologic role of these drug-metal complexes. The other major area in the laboratory revolves around the enzymatic defenses of mammalian cells against free radical attack. In the process, the investigators appear to have discovered a new family of peroxidases which they are in the process of purifying and characterizing. Projects are available investigating the role of these enzymes in the detoxification of drug-induced free radicals. State-of-the-art high-resolution NMR and ESR equipment is available in the branch and is currently being used to study the chemistry and three-dimensional structure of the interaction of adriamycin with DNA and other targets.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Hypertension-Endocrine Branch
Section on Biochemical Pharmacology
Ingeborg Hanbauer, Ph.D.

Work in this laboratory focuses on regulation of the release of catecholamines and enkephalin-like peptides from adrenal glands. The effects of electrical stimulation of the splanchnic nerve, and those of specific agonists and antagonists of GABA-ergic nicotinic or opiate receptors, on the release of the met-enkephalin-like peptides, epinephrine, and norepinephrine are investigated. The peptides released from the adrenal chromaffin cells into the adrenal venous blood are characterized by high pressure liquid chromatography and radioimmunoassay using specific antibodies.

Ongoing work also focuses on pharmacological and biochemical aspects of the regulation of striatal dopamine receptors. The regulation of dopamine receptors is studied in the corpus striatum, with particular attention on two functional states, sub- and supersensitivity. These studies comprise measurements of dopamine recognition sites, G/F protein, adenylate cyclase, calmodulin, and phosphorylation and dephosphorylation of membrane proteins and protein kinases. Furthermore, studies are carried out on the regulation of nitrendipine- and verapamil-sensitive Ca^{2+} channels in various brain areas. This work pursues the

isolation and characterization of recognition sites for these ligands and of endogenous ligands acting on these recognition sites.

Laboratory of Biochemical Genetics
Section on Molecular Biology
Marshall W. Nirenberg, Ph.D.

Basic problems in molecular biology and biochemistry, particularly those that pertain to the development of the nervous system, are studied in this section. Current research is focused on elucidating mechanisms that regulate gene expression using recombinant DNA techniques. Polyclonal and monoclonal antibodies are being used to detect protein whose expression is dependent on cloned DNA. Cultured cells are used in many studies. Research also is being conducted on cyclic nucleotides, receptors, and ion channels.

Laboratory of Biochemical Genetics
Section on Macromolecules
Alan Peterkofsky, Ph.D.

This section is concentrating on studies of cellular control mechanisms in *Escherichia coli*. One area of interest concerns the control of the synthesis and metabolism of cyclic AMP in bacterial cells. Current information suggests that cyclic AMP concentrations in *Escherichia coli* are controlled by cellular metabolites by a mechanism similar in some respects to that by which hormones affect cyclic AMP levels in many mammalian cells. The laboratory is using biochemical and recombinant DNA approaches to study the regulation of expression of the gene for adenylate cyclase as well as the factors that regulate the enzyme's activity. Another focus of attention is the *Escherichia coli* cyclic AMP receptor protein. Analyses of structure, function, and repression mechanisms involving this protein are under way.

Laboratory of Chemical Pharmacology
Section on Drug-Enzyme Interaction
James R. Gillette, Ph.D.

Various aspects of drug disposition are investigated, including the relationship between drug metabolism and drug toxicity. The main objective of this section has been the elucidation of the mechanisms of drug metabolism by enzyme systems in liver microsomes, the factors that control the activity of these systems, and the importance of these enzymes in converting inert substances to alkylating agents and other biologically active metabolites. The section also studies ways of extrapolating data obtained with liver microsomes to the cellular and animal levels.

Laboratory of Chemical Pharmacology
Section on Cellular Pharmacology
Michael A. Beaven, Ph.D.

This section studies drug action at the cellular level. Current work includes: studies on the mechanism of mast cell/basophil degranulation, particularly on the interrelationship of signals generated by Ca^{2+} fluxes and breakdown of inositol phospholipids; studies with purified and cultured populations of cells from gastric mucosa and blood vessels to determine the biochemical responses to histamine and other active hormones; and research on the release and metabolism of histamine and other active factors during inflammatory and allergic reactions.

Laboratory of Chemical Pharmacology
Section on Pharmacological Chemistry
Lance R. Pohl, Pharm.D., Ph.D.

This section studies the mechanisms of metabolism, action, and toxicity of pharmacologically active chemicals. It includes studies of the identification of active substances formed in the body, the biochemical basis of their pharmacological and toxicologic actions, and the characterization and regulation of the enzymes that either produce or metabolize these agents. This section is particularly interested in the mechanism of drug-induced autoimmune diseases. In addition, it is involved in the study of the mechanism and regulation of the turnover of cytochromes P-450 in the liver, adrenals, testes, and ovaries.

Laboratory of Molecular Hematology
W. French Anderson, M.D.

This laboratory studies the mechanism and regulation of mammalian gene expression, using hemoglobin biosynthesis as one of its primary models. The major objective is to develop the understanding and techniques necessary to carry out gene therapy for human genetic diseases. Major areas of research include: gene cloning and gene transfer, retroviral vector development, isolation and characterization of *trans* factors involved in gene expression, and drug-induced (5-azacytidine, hydroxyurea, cytosine arabinoside, etc.) alteration of globin gene expression by examination of the mechanism of action of these agents.

Laboratory of Cellular Metabolism
Martha Vaughan, M.D.

Using techniques of molecular genetics, biochemistry, and cell biology, this laboratory conducts research directed toward understanding the regulation of cyclic nucleotide synthesis and degradation. Cyclic AMP synthesis by the membrane-associated adenylate cyclase complex is controlled by stimulatory and inhibitory agonists (e.g., hormones, drugs) acting through cell-surface receptors. Signals generated by receptor-agonist interaction are transmitted to the cyclase catalytic unit via GTP-binding coupling proteins, which are targets for covalent modification (ADP ribosylation) catalyzed by bacterial toxins (e.g., cholera toxin, pertussis toxin) that activate the cyclase. Areas of current interest include: (1) molecular biology: isolation of cDNA's and genes for the regulatory components of adenylate cyclase, analysis of mRNA content and structure in differentiating systems; (2) membrane biochemistry: molecular mechanisms for the interaction of adenylate cyclase components (e.g., studies with site-specific monoclonal antibodies, reconstitution of purified proteins) and effects of toxin-catalyzed ADP ribosylation on the interaction of coupling proteins with receptors and the cyclase catalytic unit; (3) cell biology: effects of hormones and toxins on cyclic nucleotide content of cultured cells; and (4) enzymology: identification of ADP ribosyltransferases and their substrates in animal cells, effects of ADP ribosylation on enzyme function, regulatory properties of the phosphodiesterases that degrade cyclic nucleotides, and mechanisms by which calmodulin modifies the activities of phosphodiesterase and other proteins with which it interacts.

Laboratory of Cell Biology
Edward D. Korn, Ph.D.

This laboratory's research is concerned with the regulation of the polymerization and enzymatic activity of actin and myosin, the two major cytoskeletal proteins of the membrane-cytoskeleton complex of nonmuscle cells. The investigators are studying the ways in which ATP hydrolysis regulates actin polymerization and how myosin phosphorylation regulates myosin polymerization, actomyosin ATPase activity, and contractile activity. These studies include active site sequence determination and structure-function relationships studied through a variety of protein physical-chemical methods. Other research involves isolating and sequencing myosin genes, with plans to undertake site-directed mutagenesis to explore further the chemical basis of actin and myosin function. Also under investigation is the action of drugs such as cytochalasin D in order to understand at the molecular level their effects on the membrane-cytoskeleton complex.

NATIONAL INSTITUTE OF ARTHRITIS, DIABETES, AND DIGESTIVE AND KIDNEY DISEASES

Arthritis and Rheumatism Branch
Section on Chemical Immunology
Henry Metzger, M.D.

This section is studying mast cell secretion mediated by the high-affinity receptor for immunoglobulin E. The studies involve isolation, characterization, and reconstitution (into liposomes) of the receptor and exploration of biochemical perturbations during triggering. This system serves as a powerful model for examining at a molecular level the proximal events in cellular secretion mediated by a cell-surface receptor.

Genetics and Biochemistry Branch
R. Daniel Camerini-Otero, M.D., Ph.D.

This laboratory studies the mechanisms of genetic recombination and gene conversion in mammalian cells, the regulation of gene expression in higher eukaryotes, and the biochemistry of nucleic acid-protein interactions. This group also conducts studies on the effects of physical and chemical agents on genetic recombination and DNA repair in mammalian cells. In several cases material from patients with genetic diseases is used to dissect the biochemical or molecular aspects of a problem under investigation. In order to carry out these studies, the techniques utilized include molecular cloning, DNA sequencing, DNA-mediated gene transfer, construction of gene fusions and recombinant DNA libraries, and a variety of other biochemical and molecular techniques.

Digestive Diseases Branch
Jerry D. Gardner, M.D.

This laboratory investigates the cellular basis of action of gastrointestinal peptides using various isolated cell systems prepared from different gastrointestinal tissues. Gastrointestinal peptides being studied are cholecystokinin, secretin, VIP, PHI, bombesin, physalaemin, substance P, ranatensin, galanin, pancreatic polypeptide, and calcitonin gene-related peptide. Isolated cell systems have been prepared for gastric chief cells,

gastric parietal cells, pancreatic acinar cells, gastrointestinal smooth muscle cells, small intestinal epithelial cells, colonic epithelial cells, hepatic parenchymal cells, and hepatic Kupfer cells. Studies of the cellular basis of action of a particular peptide include receptor identification; development of receptor-specific antagonists; exploration of the intracellular sequence of messenger action; and the relation among the final response, receptor occupation, and messenger variation.

Molecular, Cellular, and Nutritional Endocrinology Branch
Section on Experimental Diabetes, Metabolism, and Nutrition
Samuel W. Cushman, Ph.D.

Insulin's fundamental action to stimulate glucose transport has recently been shown to occur in the rat adipose cell model system through a rapid and reversible exocytic-/endocytic-like subcellular cycling of glucose transporters between a large intracellular pool and the plasma membrane. Insulin also stimulates the appearance of cell-surface insulin-like growth factor II (IGF-II) receptors and concomitantly induces insulin receptor internalization through similar rapid and reversible membrane translocation processes. Using biochemical, cell biological, and immunologic laboratory techniques, the section: (1) investigates the structure, function, and biosynthesis of integral membrane proteins involved in the hormonal regulation of carbohydrate and lipid metabolism, especially the receptors for insulin and IGF-II and the glucose transporter; (2) studies the molecular and cellular basis of hormone action, especially relating to the mechanism of insulin action and its counterregulation by catecholamines, other peptide hormones, and the glucocorticoids; and (3) examines the influence of altered metabolic and nutritional states on cellular function and its regulation by hormones, especially those states associated with perturbed insulin action such as diabetes, obesity, and altered dietary carbohydrate and fat intake.

Molecular, Cellular, and Nutritional Endocrinology Branch
Section on Growth and Development
Matthew M. Rechler, M.D.

The laboratory uses approaches of molecular and cellular biology to define the role in normal and pathologic cell growth of a family of polypeptides, the insulin-like growth factors (IGF), present in plasma and chemically related to insulin. IGF receptors, actions, carrier proteins, and the regulation of IGF gene expression are studied in appropriate model systems. The role of IGF-II in fetal growth and development and in central nervous system function are areas of current interest.

Clinical Endocrinology Branch
Jacob Robbins, M.D.

The laboratory is engaged in studies related to the thyroid gland and thyroid hormones. The subjects of greatest interest have been thyroglobulin and related iodoproteins, the plasma transport proteins for thyroid hormones, the mechanism of entry of thyroid hormones into target cells, the metabolism of the hormones in tissues, and, on a clinical level, the management of thyroid neoplasms. In recent years, fellows have worked on the monodeiodination reaction responsible for the conversion of thyroxine to the active hormone, triiodothyronine, in liver cells; on energy-dependent transport of triiodothyronine and thyroxine into hepatocytes and into skeletal muscle, employing whole-organ and cultured-cell systems; and on the effect of lithium ion in slowing the release of thyroid iodine and lithium's use as an adjuvant in treating thyroid carcinoma with radioiodine. A current interest within the laboratory is to employ a continuous cell line of rat myoblasts to study the transport, metabolism, and actions of thyroid hormones in relation to myoblast differentiation.

Clinical Endocrinology Branch
Section on Endocrine Biochemistry
Jan Wolff, M.D., Ph.D.

The laboratory investigates cytoskeletal (especially microtubule) interactions with cell membrane functions, particularly adenylate cyclase. This involves tubulin chemistry, regulation of microtubule polymerization by associated proteins, calcium/calmodulin, and charge-charge effects, as well as the mechanism of action of antimicrotubule drugs. The laboratory is also studying regulation of membrane-bound and soluble adenylate cyclases by hormones, calmodulin, bacterial toxins, guanine nucleotide binding proteins including tubulin, and phospholipids. The goal is to understand the reciprocal regulation of these two components.

As an outgrowth of this work, the laboratory is studying adenosine receptors and antagonists, the role of bacterial adenylate cyclases as virulence factors (along with toxins), their mechanism of activation, and their method of entry into host cells.

Metabolic Diseases Branch
Molecular Pathophysiology Section
Allen M. Spiegel, M.D.

A family of guanine nucleotide binding proteins (G proteins) transduces signals across membranes by coupling receptors to effector enzymes. Distinct G proteins couple: (1) receptors for hormones and neurotransmitters that stimulate or inhibit cAMP formation; (2) rhodopsin, a photon receptor, to a cGMP phosphodiesterase; and (3) receptors for agonists that stimulate phosphatidylinositol turnover. The Molecular Pathophysiology Section studies the structure and function of G proteins. G proteins that have been purified and used for the production of antibodies have proved useful for studies of G protein structure, for immunocytochemical studies, for regional localization of G protein in brain, and for quantitation of G proteins as a function of cell differentiation. The laboratory studies states of altered target cell responsiveness for possible quantitative or qualitative changes in G proteins. Thus, a human genetic disorder characterized by generalized hormone resistance has been shown to result from a deficiency in the G protein linked to adenylate cyclase stimulation. The laboratory also searches for novel G proteins involved in membrane transduction. Such a protein has been identified in human neutrophils. In addition, cDNA probes are employed to study alterations in G protein structure and synthesis.

Diabetes Branch
Phillip Gorden, M.D.
Jesse Roth, M.D.

The Diabetes Branch studies receptors for peptide hormones, especially for insulin and insulin-like growth factors. Current projects are focused on the role of receptors and receptor antibodies in disease states, genetic disorders of the insulin receptor (including molecular biology of the receptor), biosynthesis of receptor components, the role of receptors in hormone action at the target cell, morphologic correlates of hormone binding to receptor (electron microscopy and immunocytochemistry), and receptors on circulating cells and cells in tissue culture. Other projects examine insulin and insulin receptors in the central nervous system; the evolutionary and embryologic origins of insulin, ACTH, somatostatin, and other peptide messenger molecules; and the role of such molecules in vertebrate embryos and in primitive (unicellular) organisms. The clinical service of the Diabetes Branch provides continuous access to patients with disorders of glucose metabolism and receptor-related disorders.

Laboratory of Biochemistry and Metabolism
William B. Jakoby, Ph.D.

This group approaches the problems of detoxication at the level of purified enzymes. Proteins are brought to the stage of homogeneity and are studied with respect to their catalytic, binding, and regulatory properties. Emphasis is on the mechanism of action of those enzymes catalyzing conjugation reactions with glutathione or adding sulfate or methyl groups. Currently, a natural inhibitor of methylation is being evaluated at both the enzyme and cell culture levels.

Laboratory of Biochemistry and Metabolism
Section on Enzymes and Cellular Biochemistry
Enrico Cabib, Ph.D.

The main interest of this laboratory lies in the molecular mechanisms of morphogenesis in eukaryotic cells. As model systems, the primary septum and the cell wall of the yeast, *Saccharomyces cerevisiae*, are currently investigated. The approach consists of studying the biosynthesis of the main structural materials—chitin for the primary septum and $\beta(1\rightarrow3)$glucan for the cell wall—at the enzymological, subcellular, and cellular levels. Since these materials impart shape to cell structures, it is expected that the information gathered in this way will give insights into the control and mechanism of shape formation. Techniques used include purification and kinetics of enzymes; isolation of subcellular structures, especially plasma membranes; electron microscopy; isolation of appropriate mutants; preparation of antibodies against polysaccharide synthetases; and cloning of the pertinent genes. Because of their potential use as antifungal agents, special attention is paid to inhibitors of the polysaccharide synthetases and to their mechanism of action.

Laboratory of Cell Biology and Genetics
Section on Cell Biology and Biochemistry
Harvey B. Pollard, M.D., Ph.D.

The primary interest of this group is in mechanisms of secretion of proteins, hormones, peptides, and transmitters from neuroendocrine and other cells using techniques of molecular biology, electron microscopy, electrophysiology, cell biology, and biochemistry. The researchers are particularly interested in secretory

processes in chromaffin cells, islets of Langerhans, platelets, and synaptosomes. Critical problems now under investigation include how secretory vesicle assembly is regulated, how cytoskeletal proteins interact with subcellular organelles, how calcium acts to fuse secretory vesicles to plasma membranes, and how the subsequent release of vesicle contents during exocytosis occurs. The approach of this laboratory is to search for special proteins and processes that could mediate such events.

Laboratory of Biochemical Pharmacology
Herbert Tabor, M.D.

Work in this laboratory is mainly concerned with the biosynthesis, metabolism, and function of various polyamines (e.g., spermidine and spermine) and amino acids. The polyamines occur in large amounts in biologic materials and are important in stabilizing various cell components such as cell membranes, ribosomes, and nucleic acids. Current work is directed toward the mechanism and *in vivo* significance of these effects. These studies provide experience with a variety of techniques (enzyme characterization, bacteriophage methodology, nucleic acid chemistry, and isotopic and nonisotopic synthesis). Special emphasis is placed on the use of plasmids and techniques involving DNA cloning, as well as on various genetic techniques in both *Escherichia coli* and yeast.

Other work includes studies on control mechanisms for other enzymes in bacteria and mammalian cell cultures, the mechanism of action of antibiotic agents, ribosome structure, and bacterial permeability. Investigations are also carried out on developmental biology and organ regeneration in the rat and aim at identifying and isolating those genes that must be expressed to attain or maintain a particular state of cell differentiation.

Laboratory of Biochemical Pharmacology
Section on the Genetics of Simple Eukaryotes
Reed B. Wickner, M.D.

This section is studying the genetic control of replication of a set of double-stranded RNA's found in virus-like particles in the simple eukaryote *Saccharomyces cerevisiae* (yeast). These double-stranded RNA's determine the "killer trait," the production of a toxin lethal to yeast not carrying the virus. The laboratory has found that replication of the double-stranded RNA genome involves a large number of chromosomal genes, several genes on the double-stranded RNA segments themselves, and a mitochondrial gene. These components show many complex functional interactions. Current work to examine the nature of these genes and the mechanisms of their interactions involves genetics, enzymology, pharmacology, molecular cloning, and molecular biology.

Laboratory of Chemistry
Section on Medicinal Chemistry
Kenner C. Rice, Ph.D.

The primary focus of this program is the chemistry of drugs which affect the central nervous system (CNS), as it pertains to study of the mechanisms of action of these agents and the physiologic functions of their recognition sites. The narcotics and their antagonists, phencyclidine (PCP), benzodiazepines, and non-nitrogenous CNS agents are of particular interest. Synthetic organic chemistry is a major and indispensible tool in the multidisciplinary approach utilized in these studies, which involve collaboration with biochemists, immunologists, and biochemical, neurochemical, and behavioral pharmacologists. An ongoing program aimed at the identification, purification, and elucidation of the structure and function of opiate receptor subpopulations in the overall modulation of the CNS requires the synthesis of new receptor ligands for several lines of investigation utilizing: (1) irreversible ligands specific for opiate receptor subpopulations; (2) high-specific-activity radiolabeled ligands for autoradiographic visualization of receptors; (3) conformationally restricted analogs of potent narcotics as topological probes; and (4) positron emission tomographic visualization of opiate receptor patterns in living brains. Similar studies of PCP recognition site(s), including efforts to identify a clinically useful antagonist of PCP, are in progress. A more classical medicinal chemical program currently in progress involves application of the recently developed NIH Opiate Total Synthesis for synthesis of previously inaccessible unnatural enantiomers of important opium derivatives with the goal of identifying new pharmacological agents and effects of opiates not mediated through the stereospecific receptors.

Laboratory of Physical Biology
Richard J. Podolsky, Ph.D.

This laboratory is concerned with the contraction of and regulatory mechanisms in muscle cells. The primary goal is to gain an understanding of the molecular basis of force

generation and shortening in muscle fibers. Present projects include one- and two-dimensional X-ray diffraction studies of intact and simplified muscle fiber preparations, correlation of filament structure derived from X-ray data with that obtained by electron microscopy, high time resolution mechanochemical studies, and radiation inactivation analysis of the physiologic function of various structural proteins.

Laboratory of Chemical Physics
Section on Macromolecular Biophysics
William A. Eaton, M.D., Ph.D.

This section studies structure-function relationships in proteins using biophysical methods. A major interest is the investigation of hemoglobin S polymerization in purified solutions and in intact red blood cells. The overall aim of this research is to obtain a quantitative description of the pathophysiology of sickle-cell disease and to design strategies for developing a specific therapy. In addition to conventional biophysical methods, a number of special techniques are employed, including microspectrophotometry, laser photolysis, and light scattering for studying the kinetics and thermodynamics of polymerization in single red blood cells. Other projects in the section include the study of oxygen binding by normal hemoglobin using time-resolved absorption spectroscopy with nanosecond pulsed lasers and molecular dynamics calculations to stimulate the motions of the individual atoms during the binding process.

Laboratory of Molecular Biology
Section on Physical Chemistry
Gary Felsenfeld, Ph.D.

This laboratory conducts research on the structure of DNA and chromatin within the eukaryotic nucleus, with particular emphasis on mechanisms of regulation of gene expression. Present studies are concerned with the isolation and characterization of specific factors that bind to the regulatory regions of genes that are being expressed, with the goals of identifying their roles in the control of expression and understanding in detail the molecular basis of that control. The laboratory also conducts physicochemical studies of DNA and its complexes with nuclear proteins. The methods used include standard techniques of molecular biology such as DNA cloning and sequencing, *Xenopus* oocyte injection, and *in vitro* transcriptional assays, as well as physicochemical methods applied to the determination of macromolecular structure and the measurement of the nature and strength of interactions between biologically important molecules.

Laboratory of Chemical Biology
Alan N. Schechter, M.D.

The major interest of this laboratory is understanding the control of differentiation and development of human erythroid cells, using cell biological and molecular genetic methods to study the control of globin gene expression. Cloned globin genes, including control regions, are being transfected into erythroid and nonerythroid eukaryotic cells in order to understand the DNA sequence-specific and intracellular soluble factors that control the sequential expression of these genes. This work has as one of its long-range goals the possibility of treating human genetic diseases by transferring new genes into cells of patients. In addition to these basic studies, clinical protocols are under way to use noninvasive modalities (e.g., NMR imaging) to evaluate disease severity and response to therapy in sickle-cell patients and to use drugs (e.g., hydroxyurea) to activate fetal hemoglobin genes in patients with hemoglobinopathies.

Laboratory of Bioorganic Chemistry
Section on Pharmacodynamics
John W. Daly, Ph.D.

This section is engaged in research on the formation, degradation, and role of cyclic nucleotides in the nervous system, including: (1) the mechanisms of action of forskolin on adenylate cyclase; (2) development of selective agonists/antagonists for receptors for catecholamines, adenosine, and other neuroregulators; (3) the relationship between membrane potential, phospholipid turnover, and generation of cyclic nucleotides; (4) the interrelationship of adenosine and calcium in the regulation of cyclic nucleotide formation and action; and (5) morphologic entities (neurosomes/gliosomes) associated with cyclic nucleotide formation and action. It also conducts research on the effect of drugs on neuronal and muscular function, in particular the transport and function of ions such as sodium, potassium, and calcium, using radioactive alkaloids such as batrachotoxin, histrionicotoxin, and pumiliotoxin to investigate sites associated with transport of such ions.

Laboratory of Bioorganic Chemistry
Section on Oxidation Mechanisms
Donald M. Jerina, Ph.D.

The primary interest of this section is the elucidation of the fundamental mechanisms by which drugs and environmental chemicals are transformed in the body. In many instances oxidative metabolism produces chemically reactive metabolites which are responsible for the cytotoxic, mutagenic, and carcinogenic activity of the drug substrate. Recent studies have been concerned with the roles of the cytochrome P-450 system and epoxide hydrolase in the formation of mutagenic and carcinogenic metabolites from the polycyclic aromatic hydrocarbons. Emphasis is on modern instrument techniques such as high pressure liquid chromatography, high resolution mass spectrometry-gas chromatography, and high resolution magnetic resonance in the study of metabolism catalyzed by homogeneous cytochromes P-450, epoxide hydrolase, and glutathione transferases.

Laboratory of Bioorganic Chemistry
Section on Neurobiology
Phil Skolnick, Ph.D.

This research program is concerned with understanding the relationship between receptors for psychoactive compounds and the endogenous substances which normally interact with these receptors. The techniques employed in studying these relationships range from biochemical investigations of the nature of endogenous ligands and their interaction with membrane receptors to the use of both primary and transformed cell culture models and classical "whole animal" pharmacology. Specific projects currently in progress include: (1) differential regulation of CNS benzodiazepine receptors by pharmacologically defined "agonists" and "antagonists;" (2) study of the role of ionophores (e.g., calcium and chloride ions) in neuronal excitability; (3) defining the physiologic role of benzodiazepine receptors found outside the CNS; and (4) the physiologic and pharmacological modulation of recognition sites and uptake systems in the CNS for psychoactive drugs (e.g., phenethylamines such as amphetamine) and the relationship of such sites to their functional role(s).

Laboratory of Analytical Chemistry
Steroid Hormones Section
S. Stoney Simons, Jr., Ph.D.

The objective of this group is to define, on a molecular level, the biological properties of the receptors for steroid hormones. Major efforts are devoted to studying the activities of glucocorticoid receptor-steroid complexes up to, and including, their effects on gene transcription. Current investigations concern the biochemistry of covalent, affinity-labeled glucocorticoid receptor-steroid complexes; purification of the covalently labeled complexes; examination of factors determining agonist versus antagonist activity for various steroid hormones in the same and different cell lines; and the nature of the biologically active nuclear binding site for receptor-steroid complexes. The experimental approaches include tissue culture, whole-cell bioassays, nucleic acid hybridization, affinity labeling, gel electrophoresis, binding to cloned DNA sequences, nuclear protein fractionation, and synthetic organic chemistry.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Laboratory of Clinical Investigation
Michael M. Frank, M.D.

The Laboratory of Clinical Investigation performs basic and clinical research on the pathophysiologic basis of disease in three general areas—allergy, clinical immunology, and infectious diseases. Ongoing investigations in allergy and immunology attempt to define the pathophysiologic basis of allergic disease in terms of the release of granular contents from mast cells; mucus secretion in the airways; control of blood flow to tissues involved in allergy, such as the nasal mucosa; excessive proliferation of cells involved in immediate hypersensitivity, as in mastocytosis; and cellular function in host defense across mucosal barriers. Studies in infectious disease examine herpes virus pathophysiology; molecular biology and the use and function of antiviral agents; host defense against fungi and the role of antifungal agents; pathophysiologic responses of the phagocytic cell and the means by which it destroys invading organisms; and the role of antibody and complement in the production of immunologic damage and in host defense against parasitic, bacterial, fungal, and viral diseases. Drug-related studies have examined the effect of glucocorticoids on the trafficking of lymphocytes; the use of androgens in the treatment of immunologic disorders, including hereditary angioedema; new antiviral agents, including acyclovir, for the treatment of herpes genitalis; and new antifungal agents such as SF 86-327. Studies of new immunomodulatory agents are ongoing. Studies of drug action are conducted

on a more basic level as well. For example, the laboratory has evaluated the usefulness of ascorbic acid *in vivo* and *in vitro* in the management of granulocyte disorders. Other studies have focused on the action of a new anticomplementary agent, K76, which has recently been shown to attenuate one type of autoimmune ophthalmitis. More basic studies in the laboratory include those on viral replication and the effects of drugs on viral replication; cell biology and the effect of drugs on endocytosis of receptors from the cell membrane as a part of the phagocytic process; the movement of receptors important for phagocytosis and chemotaxis from granular compartments to the cell surface; the effects of drugs on mucus synthesis and secretion by the airways (mucus formation represents a major factor in the pathophysiology of asthma); and agents that affect mast cells and antihistaminic reagents in mastocytosis.

Laboratory of Immunogenetics
Thomas J. Kindt, Ph.D.

The principal focus of this laboratory is on the structure and regulatory interactions of cell-surface molecules encoded by the major histocompatibility complex (MHC) and other cell-surface molecules important in the functioning of the immune system. Using the methods of molecular biology, genes encoding relevant molecules are identified for study and cloned and sequenced as necessary. Studies are designed to determine the function of individual molecules, particularly those encoded within multigene families. Molecular interactions of cell-surface receptors with target complexes on other cells and with soluble factors which trigger, suppress, or modify immunologic reactivity are studied in the intact cell and in artificial environments constructed by transfection of isolated genes. Examples of current projects are: the role of DNA methylases and DNAse hypersensitive sites in the regulation of immunoglobulin expression; tissue-specific and locus-specific regulation of class II MHC antigen expression in humans and rabbits; and variable gene processing leading to the synthesis of multiple products from one class I MHC gene and the influence of these diverse products on class I-mediated functions.

Laboratory of Immunoregulation
H. Clifford Lane, M.D.

This laboratory is involved in the study of human immune responses in normal and disease states. A major focus of the laboratory is in the area of B-cell activation and immunoregulation, employing the techniques of cell culture, purification of lymphokines, identification of cell-surface receptors, protein sequencing, and gene cloning. A recent addition to the laboratory has been expertise in the area of cultivation of the AIDS retrovirus, HTLV-III/LAV. In addition to basic research on human immune responses in normal and disease states, the laboratory also participates in an active clinical research program investigating the immunopathogenesis of a variety of inflammatory and immunodeficiency diseases. The laboratory has a large clinical research program involved in studying and treating patients with acquired immune deficiency syndrome (AIDS) and related diseases. Clinical trials are currently under way involving both anti-retroviral agents and immunomodulatory therapy, including bone marrow transplantation, interleukin-2, and interferon.

Laboratory of Viral Diseases
Bernard Moss, M.D., Ph.D.

This is a molecular biology laboratory that carries out fundamental research on the structure of viruses, the replication and expression of viral genomes, the interactions of viruses with host cells, and the factors associated with virulence in experimental animals. Genetic engineering is used to develop new approaches to the prevention and treatment of viral diseases. Determination of the mechanisms of action of antiviral agents and the construction of live recombinant vaccines are additional areas of current investigation.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Office of the Scientific Director
Section on Growth Factors
Gordon Guroff, Ph.D.

Investigators in this section are interested in the biochemical and physiologic actions of nerve growth factor. This factor has been studied for many years and its function is now clear: it is required for the development and survival of the sympathetic and sensory nervous systems. Without nerve growth factor, these neurons die. The chemistry of nerve growth factor has been completely elucidated, but its mechanism of action, and indeed the mechanisms of action of the more than 30 other growth factors now known, are only dimly perceived.

This group's work involves a dissection of the biochemical events, particularly those in the nucleus, which follow the interaction of nerve growth factor with the cell. The systems used are organ cultures of sympathetic ganglia from neonatal animals and the PC12 cell, a pheochromocytoma clone which differentiates *in vitro* into a sympathetic neuron in response to nerve growth factor. In recent years, it has become clear that phosphorylative changes in the proteins of these cells are pivotal events in the actions of the factor. The laboratory is working to isolate and purify the proteins involved and the enzymes carrying out these phosphorylations, as well as to understand the role of these proteins in the structure and transcription of the DNA. The ultimate goal is to define the exact molecular mechanism of these peptide factors. Research is also in progress on the induction of transmitter-synthesizing enzymes, the enzymology of neurite development, and the actions of growth factors on the central nervous system.

Laboratory of Theoretical and Physical Biology
David Rodbard, M.D.

This laboratory studies receptors for hormones and neuropeptides *in vitro*, and analyzes pharmacokinetic processes *in vivo* using stable isotopes with liquid chromatography-mass spectrometry.

The Section on Theoretical Biology studies drug-receptor interactions, combining experimental and computer-modeling approaches, including computer-assisted optimization of experimental design. The multiple types and subtypes of the opiopeptide receptor system are the present focus of attention.

The Section on Metabolic Analysis studies the metabolism of calcium, other metals, carbohydrates, steroids, and amino acids in humans to evaluate metabolic correlates of growth and development (e.g., effects of growth hormone, sex steroids, and pregnancy).

The Section on Macromolecular Analysis develops new methods for fractionation of proteins and polypeptides, using electrophoretic and other physical-chemical methods.

Laboratory of Neurochemistry and Neuroimmunology
Harold Gainer, Ph.D.

This laboratory investigates the biosynthesis, secretion, and mechanisms of action of various biologically active neuropeptides such as ACTH, α-MSH, β-endorphin, dynorphin, vasopressin, and oxytocin. Techniques employed include immunochemistry, immunoassay, immunocytochemistry, recombinant DNA methodology, protein and peptide separation and chemistry, and microchemistry of small brain areas. The laboratory uses the approaches of cell biology to study the intracellular and extracellular mechanisms which determine the expression of specific neuronal identity (i.e., the neuron's endogenous peptides, particular projection pathways, and specific termination sites in the central nervous system). Also studied is the development of peptidergic neurons and their relation to the immune system.

Cell Biology and Metabolism Branch
Richard D. Klausner, M.D.

This laboratory focuses on various areas of receptor and membrane biology. One program is aimed at understanding the molecular nature of the transcriptional control elements that determine the expression of the highly regulated human transferrin receptor. Basic techniques of recombinant DNA technology have been employed to clone the gene for this receptor and to analyze the sequences involved in the sensitivity of this gene to pharmacological agents that alter iron availability as well as to growth factors and the state of proliferation of the cell. This highly regulated receptor serves as a model for the molecular aspects of receptor regulation. Two groups are examining the role of specific receptors in the activation and proliferation of T cells. One is studying the structure and function of the murine T cell antigen receptor. This includes the identification, characterization, and purification of each of the six different chains of the receptor complex. Purification is permitting the sequencing of these proteins, which will allow the molecular cloning of the genes encoding the components of the receptor complex. The structure of the complex in different classes of T cells, during T cell development, and in abnormal T cells is being explored. The receptor undergoes a complex pattern of phosphorylation events upon ligand binding. The nature and function of these events are being dissected by structural and pharmacological approaches, and correlations between receptor phosphorylation, phospholipid turnover, calcium fluxes, and membrane potential are active areas of investigation. The interleukin-2 receptor drives T lymphocyte proliferation in response to the lymphokine IL-2. The gene encoding this receptor has been cloned and the promoter and regulatory regions are being characterized. Particular

attention is being focused on understanding the expression of this gene in normal and leukemic T cells. The approaches in the laboratory include lipid and protein biochemistry, immunology, hybridoma technology, recombinant DNA technology, and cell biology.

Endocrinology and Reproduction Research Branch
Kevin J. Catt, M.D., Ph.D.

This branch conducts research into basic aspects of hormone action, with emphasis on the characterization and regulation of cell-surface receptors for peptide hormones and their associated membrane effector systems. Of particular interest are the receptor-mediated mechanisms involved in the regulation of pituitary, gonadal, and adrenal function. Current research includes studies on the receptors and mechanisms of action of hypothalamic and pituitary hormones, and on the control of steroid production in endocrine target cells of the gonads and adrenal glands. The role of hormones in cellular regulation is also examined in relation to normal and disordered human endocrine function, using *in vitro* systems for the analysis of hormone action and the stimulatory and inhibitory control of target-cell function. Specific areas of study include the role of neuropeptides in hypothalamic-pituitary regulation; the analysis of brain receptors for peptide hormones (angiotensin II, GnRH, and CRF); the isolation of receptors for angiotensin, GnRH, and gonadotropins; the hormonal control of granulosa-cell differentiation and Leydig cell function; the renin-angiotensin system and aldosterone secretion; and the phosphorylation mechanisms involved in hormonal and metabolic regulation.

Laboratory of Developmental Neurobiology
Phillip G. Nelson, M.D., Ph.D.

Research in neurobiology is conducted using tissue cultures of normal and neoplastic nerve and muscle. The analysis of the membrane mechanisms of action of neurotransmitters and other neuroactive compounds is a primary aim. A number of biochemical studies of long-term interneuronal interactions related to synaptogenesis are in progress. The membrane mechanisms of action of some neuroactive peptides are under investigation. In addition, molecular genetic techniques are being applied to problems of nervous system development.

Laboratory of Developmental Neurobiology
Section on Neuroendocrinology
David C. Klein, Ph.D.

Investigations in this section focus on the molecular mechanisms through which neurotransmitters regulate gene expression, using cultured pinealocytes as the primary experimental model. There are three areas of activity. First, the adrenergic control of pineal cyclic AMP and cyclic GMP is studied; both cyclic nucleotides are regulated by α-adrenergic potentiation of β-adrenergic stimulation. Second, the role of membrane protein phosphorylation in transsynaptic signal transduction is investigated. And third, recombinant DNA techniques are being used to study how enzymes involved in the conversion of tryptophan to melatonin are regulated.

Laboratory of Developmental Pharmacology
Daniel W. Nebert, M.D.

This laboratory investigates gene expression, with special emphasis on enzymes that metabolize drugs, chemical carcinogens, and other environmental pollutants. Molecular genetic and recombinant DNA techniques are used to study differences in the expression of these genes among inbred mouse strains, as well as wild-type and variant cells in culture. Nucleotide and amino acid sequences, evolution, tissue and developmental specificity, the role of enhancer sequences, and DNA-binding regulatory proteins such as inducer-receptor complexes are examined to learn about fundamental mechanisms involving drug metabolism induction, drug toxicity and teratogenesis, and chemical tumorigenesis and mutagenesis. One long-range goal is to develop recombinant DNA assays for predicting human populations at increased risk for certain types of environmentally induced toxicity, birth defects, and cancers.

NATIONAL INSTITUTE OF DENTAL RESEARCH

Laboratory of Microbiology and Immunology
Cellular Immunology Section
Sharon M. Wahl, Ph.D.

This section investigates basic mechanisms by which host defenses to microbial and other antigens mobilize and modulate cellular and antibody-mediated inflammatory reactions. A major effort involves the study of hormone-like immunoregulatory factors produced by inflammatory cells. The biologic effects and biochemical and molecular

characteristics of these inflammatory hormones which are produced by lymphocytes and monocytes and are active at 10^{-10} to 10^{-15} M are being explored. The section is using mediators such as interferon, interleukin 1 and 2, fibroblast activating factor, oxygen metabolism-inducing factors, colony stimulating factor, prostaglandins, thromboxanes, and leukotrienes to modulate inflammatory cell responses *in vitro* and to define mechanisms of immune regulation of connective tissue metabolism. Through the use of pharmacological agents and monoclonal antibodies, it is dissecting the mechanisms by which these mediators activate target cells and initiate the cascade of reactions which amplify the inflammatory process.

Studies of the immunological events associated with AIDS, rheumatoid arthritis, streptococcal cell wall-induced polyarthritis in a rat model, and periodontitis analyze the mechanisms of chronic inflammatory disease and how the course of the disease can be altered by manipulation of the immune system (using steroids, nonsteroidal anti-inflammatory drugs, cyclosporin, etc.). Additionally, the use of the mononuclear cell-derived hormone-like mediators (IL-2, interferon) in the treatment of diseases such as cancer and AIDS is currently being evaluated clinically and immunologically.

Laboratory of Developmental Biology and Anomalies
George R. Martin, Ph.D.

This laboratory studies the synthesis and degradation of connective tissue and disorders and drugs that alter its normal structure and function. Mouse models of human diseases (such as diabetes, cancer cell metastasis, oral-facial malformation, and brittle bone) are studied and also used as test systems to monitor potential therapeutic approaches. Differentiating cultured cells are used to detect and investigate the teratogenic action of drugs. Particular attention is directed toward genetic and environmental factors which alter the expression of connective tissue genes using recombinant DNA technology.

Neurobiology and Anesthesiology Branch
Ronald Dubner, D.D.S., Ph.D.

This branch conducts studies on the neurobiologic basis of somatic sensation, with emphasis on pain mechanisms. Neuropharmacological studies examine changes in neurochemical activity at various levels of the nervous system following the production of experimental inflammation in animals. Neurocytochemical studies examine the neuronal circuitry in the medullary and spinal dorsal horns, utilizing immunocytochemical and autoradiographic techniques at the light and electron microscope level to identify putative neurotransmitters localized to these regions. Electrophysiologic studies are concerned with the functional characteristics of single cells in the dorsal horn and their role in the coding of pain, temperature, and tactile information. In behavioral studies, monkeys are trained to discriminate noxious and innocuous thermal stimuli, and behavioral events are correlated with single-unit activity in the dorsal horn. The effects of opiates, monoamines, and other putative neurotransmitters in the brain on neural function and animal behavior are studied utilizing this behavioral model.

The clinical program of this branch conducts research on pain assessment and evaluates various pharmacological agents utilized in the control of acute and chronic pain. Present studies include the role of endogenous opioid compounds in stress and analgesia, the mechanism of action and efficacy of tricyclic antidepressant drugs in the control of painful neuropathies, the efficacy of different opiate receptor agonists in the treatment of cancer pain, and the analgesic potency of nonsteroidal anti-inflammatory drugs.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

(These laboratories are located in Research Triangle Park, North Carolina)

Laboratory of Behavioral and Neurological Toxicology
Clifford L. Mitchell, Ph.D.

The research programs of the laboratory are aimed at understanding neuronal plasticity and nervous system mechanisms responsible for adaptation to the environment. This is of particular relevance to toxicology since interference with adaptive mechanisms gives rise to the signs and symptoms produced by a toxicant. An interdisciplinary approach to these problems is taken utilizing behavioral, neurochemical, neurophysiologic, and neuropathologic techniques. Particular emphasis is placed on the behavioral, neurochemical, and electrophysiological indices of neural plasticity and adaptation during the development of the nervous system, and their alteration by exposure to environmental agents. Among the substances being studied are heavy

metals, organochlorine pesticides, microwaves, and their interactions with psychoactive drugs.

Laboratory of Molecular Biophysics
Colin F. Chignell, Ph.D.

Research programs of the laboratory cover several areas, including the use of physicochemical techniques to monitor the interaction of chemical agents with biologic systems; physical organic and bio-organic chemical studies of environmental agents, biologic materials, and their conversion products; and the development and application of mass spectrometry to the identification and quantitation of chemical agents and their metabolites in biologic systems. The molecular biophysics program mainly focuses on the use of sophisticated spectroscopic techniques (ESR, NMR, fluorescence and absorption spectroscopy, CD) to monitor the interaction of environmental agents with biologic systems. Current projects include the generation of free-radical intermediates during the metabolism of xenobiotics and the mechanisms of chemically induced photosensitization (phototoxicity and photoallergy). In addition, NMR spectroscopy is being used to study the effects of environmental agents on metabolism and the biotransformation of chemical compounds *in vivo*. An important component of this program is an NMR imaging system which makes it possible to monitor the response of experimental animals to toxic chemicals. Other programs include the biochemistry of prostaglandins and leukotrienes (including the co-oxidation of carcinogens by prostaglandin synthetase and peroxidases); and the metabolic transformation of phthalate esters. The mass spectrometry laboratory is well equipped. Current research in this area includes the analysis of peptides and oligonucleotides by tandem mass spectrometry, the development of combined liquid chromatography-mass spectrometry for the analysis of environmental chemicals and their metabolites, and the application of tandem mass spectrometry to gas phase ion chemistry.

Laboratory of Pharmacology
Molecular and Comparative Pharmacology Section
John R. Bend, Ph.D.
Richard M. Philpot, Ph.D.

Research in this section is directed toward understanding the relationships between the metabolism of chemicals and cell-selective toxicity in liver and various extrahepatic tissues, particularly those of the lung. Biochemical (including molecular biology), chemical, immunochemical, pharmacological, and pharmacokinetic concepts are used to elucidate the mechanisms by which environmental contaminants exert their toxicologic effects. An integrated experimental approach is often used in these studies (e.g., intact animals, isolated perfused organs, enriched populations of freshly isolated cells, cells in culture, subcellular fractions), although experiments are most frequently performed with purified enzymes (various isozymes of cytochrome P-450, glutathione S-transferase, and UDPGA-glucuronosyltransferase). Emphasis is currently being given to the characterization of isozymes of important xenobiotic-metabolizing enzymes found in lung tissue, their cellular distribution, their regulation, and their role in the biotransformation of both endogenous and exogenous chemicals.

Laboratory of Pulmonary Function and Toxicology
Paul Nettesheim, M.D.

The research programs of the Laboratory of Pulmonary Function and Toxicology are concerned with the study of the cellular and biochemical basis of normal and abnormal lung functions. Special areas of emphasis are: (1) regulation of biosynthesis and secretion of mucous glycoproteins; (2) metabolism of prostaglandins in the lungs and the effect of prostaglandins on some metabolic functions of the lung; (3) the composition, secretion, and function of the noncellular alveolar lining layer, particularly its protein components, and disturbances of the noncellular alveolar lining layer in disease; (4) the biology, life cycle, and function of respiratory tract epithelial cells studied with *in vivo* and *in vitro* techniques; (5) the mechanisms of toxicity of airborne particles and fibers on lung tissues and the mechanisms of toxicity of asbestos studied *in vivo* and *in vitro*; and (6) mechanisms of respiratory tract carcinogenesis, the development of neoplastic disease, *in vitro* epithelial cell transformation and promotion studies, and mechanisms of cocarcinogenesis and promotion.

Laboratory of Reproductive and Developmental Toxicology
Developmental Endocrinology and Pharmacology Section
John A. McLachlan, Ph.D.

Investigators in this section study the biology and chemistry of estrogens and estrogenic xenobiotics. A primary interest is the normal and abnormal influences of estrogens on target cell differentiation; permanently altered programs of cell differentiation include atypical

expression of gene products and abnormal growth regulation. Studies routinely use fetal or immature mice, organ cultures of fetal target tissues, and primary cultures of epithelial or mesenchymal target cells. Cell cultures are used to determine the mechanisms of estrogen-induced neoplastic cell transformation. Areas of interest include genital tract pathobiology, hormone-associated growth factors, hormone-induced gene action, regulation of cell proliferation, estrogen receptors, structure-activity relationships of estrogenic chemicals, and target organ metabolism of estrogens.

Laboratory of Reproductive and Developmental Toxicology
Experimental Teratogenesis Section
Robert M. Pratt, Ph.D.

Studies in this section deal primarily with rodent embryonic and fetal development and the mechanisms by which various environmental agents and drugs interfere with normal development. Emphasis is placed on the development of the craniofacial region and the biochemical and molecular bases for sensitivity to teratogens using cell, organ, and whole-embryo culture in conjunction with biochemical, morphologic, pharmacological, and toxicologic approaches. Of special interest is the manner in which various hormones and growth factors (EGF) influence normal and abnormal development of embryonic and fetal tissues. Also of interest are the biochemical and molecular factors predisposing embryos to the teratogenic effects of agents such as steroids, retinoids, and dioxins (TCDD).

Laboratory of Reproductive and Developmental Toxicology
Reproductive Neuroendocrinology Section
Andres Negro-Vilar, M.D., Ph.D.

Research in this section is directed toward understanding and defining the endocrine, paracrine, and autocrine roles of peptides and amines within the hypothalamic-pituitary-gonadal axis. Several levels of integration are considered. At the subcellular level, the mechanisms involved in modulation of peptide hormone release are evaluated by analyzing activation of aminergic receptors, membrane phospholipid breakdown, calcium mobilization, and activation of other intracellular messenger systems, and correlating those events with peptide hormone release. At the cellular level, potentiation or cooperation between peptides and amines to modify hormone release is also studied. *In vivo* studies include an analysis of the neurotransmitters and modulators that regulate or modify the pulsatile secretory pattern of different peptide hormones, definition of the role of opioid peptides in the regulation of pituitary and gonadal function, and investigation of the effects of stress or selected neurotoxins on central monoamine metabolism and in the secretion of pro-opiomelanocortin-derived peptides and other pituitary hormones.

Membrane Transduction Section
Martin Rodbell, Ph.D.

This section carries out research on the molecular basis for the actions of hormones, neurotransmitters, and other biologic agents that act through cell membrane receptors. Such research covers the isolation and characterization of membrane components involved in signal transduction, including their ultrastructure, topography in membranes, and functions.

NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE

Laboratory of Neurophysiology
Jeffery L. Barker, M.D.
Thomas G. Smith, Jr., M.D.

The principal aim of this laboratory is a multidisciplinary analysis of the cellular properties of specific CNS neurons and the pharmacological effects of clinically important drugs on these properties. Most of the research is conducted using monolayer cultures of neurons dissociated from different regions of the embryonic CNS. The methods employed are primarily electrophysiologic, including intracellular recording and voltage-clamp and patch-clamp techniques, although other methods, including biochemical and morphologic approaches, are also utilized. Specific projects include the comparison of chemically and electrically excitable membrane properties in CNS neurons and the effects of clinically important drugs on these properties, the identification of specific cell types using immunohistochemical and biochemical methods, and the separation of specific populations of neurons using fluorescence-activated cell-sorting techniques.

Laboratory of Experimental Neuropathology
Henry deF. Webster, M.D.

The Cellular Neuropathology Section conducts research on cellular and subcellular mechanisms of myelin

formation and maintenance. It develops and uses a broad range of techniques to identify abnormalities in myelin structure, chemistry, and function that lead to myelin breakdown of the type seen in multiple sclerosis, other demyelinating diseases, and experimental myelin lesions. It also investigates cellular mechanisms of myelin regeneration, especially those relevant to the central nervous system.

The Neurotoxicology Section conducts basic research on toxins which induce disease or malfunction of the central and peripheral nervous systems. Among its goals are to elucidate cellular and subcellular mechanisms of neurotoxin actions and to develop correlations between neurotoxicity and dysfunctions in behavior and biochemistry. Researchers in this section investigate toxic mechanisms of neurological disease, conducting collaborative studies with other clinical or basic science components of the National Institute of Neurological and Communicative Disorders and Stroke as appropriate. Finally, this group utilizes neurotoxins to develop animal models of neurological disorders.

Developmental and Metabolic Neurology Branch
Section on Membrane Biochemistry
Peter H. Fishman, Ph.D.

This section's research involves the biosynthesis, organization, and function of cell-surface membrane components. Of major interest are the mechanisms by which cells receive, process, and attenuate external signals. The hormone-stimulated adenylate cyclase system is used as a model for transmembrane signaling. Hormones are recognized by specific receptors on the external side of the plasma membrane; following hormone binding, there is a transduction process which leads to stimulation of adenylate cyclase on the cytoplasmic side of the membrane. Prolonged stimulation results in both desensitization, where the transduction process becomes attenuated, and in down-regulation, where the receptors become internalized and degraded. The section also is exploring the biosynthesis and function of complex glycosphingolipids known as gangliosides. Gangliosides can function as receptors for bacterial toxins and may be biotransducers of both positive and negative signals which regulate cell growth and differentiation.

Experimental Therapeutics Branch
Pharmacology Section
Thomas N. Chase, M.D.

Clinical and preclinical studies are directed toward the development of improved therapies for dementing and extrapyramidal diseases. Transmitter pharmacology strategies concentrate on the dopamine system and closely interactive peptidergic pathways. Information from positron emission tomography allows the localization and biochemical characterization of brain transmitters. These findings give rise to pathogenetic hypotheses, linking an abnormality in a specific transmitter system with the presence of a particular neurological sign. Following evaluation in various animal models as well as in patients using selective pharmacological probes, such hypotheses motivate the design of novel pharmaceutical interventions for preclinical studies and clinical trials. Current preclinical projects include biochemical and behavioral studies of dopamine-cholecystokinin system interactions; synthesis and testing of the selective inhibitors of cholecystokinin-octapeptide degrading enzyme; and examination of the effects of selective D-1 or D-2 dopamine agonists and antagonists on motor behavior and central dopaminergic and nondopaminergic mechanisms. Ongoing clinical projects include mapping of cerebral muscarinic receptors in Alzheimer's disease under basal conditions and in response to cholinergic agonists; evaluating the effects on cognitive and motor function of a drug which depletes brain somatostatin; and pharmacokinetic and pharmacodynamic studies of the on-off response in parkinsonian patients.

Experimental Therapeutics Branch
Physiological Neuropharmacology Section
Judith R. Walters, Ph.D.

Studies in the Physiological Neuropharmacology Section are directed toward investigation of the effects of drugs on neuronal activity and neurotransmitter function in the CNS, especially in the basal ganglia and associated areas, including the substantia nigra, striatum, and globus pallidus. Extracellular single-unit recording procedures and iontophoretic techniques are employed to explore the effects of drugs and neurotransmitters on the activity of single neurons *in vivo* in the anesthetized rat, and *in vitro* in brain slices. Currently, the functions of dopamine, GABA, and peptide-containing neurons in these brain regions are being investigated, with special focus on modulatory interactions between different

neurotransmitter systems and the consequences of agonist and transmitter-induced stimulation of specific transmitter receptor subtypes. Neurophysiologic determinations are combined with chronic or acute drug treatment, administration of selective lesions, and assessment of biochemical parameters of transmitter function.

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

Laboratory of Clinical Studies
Markku Linnoila, M.D., Ph.D.

The laboratory consists of a 10-bed research ward, 11 modules of laboratory space, and an animal facility in the NIH Clinical Center. There are five sections and two units in the laboratory. The major research interests consist of treatment and prevention of alcoholism and alcohol withdrawal. New medications with specific mechanisms of action will be tried in detoxication and maintenance treatments of alcoholics. Both the pharmacokinetics and pharmacodynamics of the drugs are carefully monitored 24 hours a day with EEG, ECG, and BP telemetry as well as temperature and activity measurements. Cerebrospinal fluid, plasma and urine monoamines, and prostaglandins are quantified with mass fragmentography and liquid chromatography. Peptide neuromodulators are measured with radioimmunoassays after separation with chromatography. Receptor functions are measured in blood cells and in animal experiments. Brain functioning is measured with electrophysiological and imaging techniques over and beyond behavioral observations. Liver functioning will be characterized using C_{13}-labeled drugs as tools to evaluate metabolic rates of both flow- and enzyme-dependent drugs. Preclinical tests of drugs having potential for treatment of alcoholism will be conducted in the Neuroscience Section of the laboratory. The Unit of Genetic Studies will use two-dimensional protein electrophoresis to detect polymorphisms in families with alcoholics and subsequently will engage in chromosomal mapping.

Laboratory of Preclinical Studies
Forrest F. Weight, M.D.

Research investigations in this laboratory center on the physiology and pharmacology of neurons and synapses in the central and peripheral nervous systems. The general areas studied include: regulation of nerve cell excitability and neurotransmitter release, cellular actions of neurotransmitters such as dopamine, acetylcholine, serotonin, and GABA; membrane mechanisms of neurotransmitter and drug actions; cellular actions of peptides such as enkephalins, endorphins, and LH-RF; identification of neurotransmitters in central synaptic pathways; and mechanisms of action of ethanol, barbiturates, opiates, and other neuroactive substances. The research techniques available to an associate include: extracellular unit recording and iontophoresis of drugs and putative transmitters to single neurons in the CNS; intracellular recording and intracellular injection techniques; use of *in vitro* preparations such as CNS slices, sympathetic ganglia, and tissue culture for studying the pharmacology of drug-receptor interactions; and voltage- and patch-clamp techniques for studying the ionic basis of membrane permeability changes involved in drug and transmitter actions.

Laboratory for Studies of Neuroadaptive Processes
Section on Neurobiology
Boris Tabakoff, Ph.D.
Paula Hoffman, Ph.D.

The research program in this laboratory is primarily concerned with mechanisms of ethanol tolerance and physical dependence. Projects include neurochemical, genetic, and behavioral analyses of these phenomena. Neurotransmitter receptor-effector coupling processes in brain and in tissue culture preparations are currently being investigated. Systems being studied are catecholamine receptors linked to adenylate cyclase, receptors coupled to phosphatidylinositol turnover, and the GABA-benzodiazepine-barbiturate receptor-chloride channel complex. Basic mechanisms of receptor binding and receptor-effector coupling are investigated, as well as the effects of acute and chronic ethanol treatments on these processes. Studies are performed in inbred strains of animals and in animals selectively bred for differing responses to ethanol.

The neuropeptide vasopressin, given exogenously, maintains ethanol tolerance, and behavioral and biochemical studies of the role of vasopressin in ethanol tolerance and physical dependence are a goal of this laboratory. Studies include determination of the importance of the endogenous peptide for neuroadaptive responses; investigation of the neurochemical mechanism by which vasopressin influences tolerance; and evaluation of the chronic effects of ethanol on brain and pituitary vasopressin biosynthesis.

Molecular genetic analysis of the alcohol-metabolizing enzymes, alcohol dehydrogenase (ADH) and aldehyde dehydrogenase, is another project in this laboratory. Studies include the derivation of probes for various isozymes of ADH, which can eventually be used to examine ADH polymorphisms in white cells from individuals with varying degrees of alcohol tolerance and susceptibility to alcoholism.

NATIONAL INSTITUTE OF MENTAL HEALTH

Laboratory of Cerebral Metabolism
Section on Developmental Neurochemistry
Louis Sokoloff, M.D.

Laboratory investigations are directed toward the biochemical aspects of growth, development, maturation, and regulation of metabolism in the CNS. These investigations are pursued at various levels, from molecular biology through enzymology and biochemistry to whole-animal physiology. Present emphasis is on the applications of a method recently developed in this laboratory that permits measurement of the rates of cerebral glucose consumption in the structural and functional components of the brain in conscious laboratory animals. This method is being applied in a variety of physiologic and pathologic states. Methods for the measurement of other biochemical processes in the brain *in vivo* are under development.

Laboratory of Molecular Biology
Section on Biophysical Chemistry
David M. Neville, Jr., M.D.

This section studies the mechanisms of action of protein toxins such as ricin, diphtheria, and tetanus toxin. Particular emphasis is given to the receptor-mediated entry processes to the cytosol compartment. These pathologic processes are viewed as analogous to physiologic protein and peptide transport thought to be involved in signaling events. In conjunction with the basic program the section designs, synthesizes, and tests monoclonal antibody-toxin conjugates (immunotoxins) for use as therapeutic reagents in eliminating unwanted cell types from mixed-cell populations. Current goals are to increase the therapeutic ratio of immunotoxins to permit *in vivo* use. Design considerations will utilize newly acquired knowledge on toxin entry mechanisms. Active collaborations with clinical groups are maintained.

Laboratory of Molecular Biology
Section on Regulatory Proteins
Werner A. Klee, Ph.D.

The major emphasis of the current program is directed toward the elucidation of the mechanism of action of opiates and the peptides that normally interact with opiate receptors. Included are studies on the isolation and characterization of opiate receptors and the regulation of adenylate cyclase activity by opiate receptors. These studies, carried out primarily with purified systems and neuronal cells in culture, are aimed at understanding opiate tolerance and dependence in biochemical terms. In addition, the interrelationships among the several components of inhibitory-receptor adenylate cyclase complexes, including especially GTP binding and hydrolyzing proteins, are being explored. The relevance of this work to the action of other CNS-active drugs and to normal brain function is also being explored.

Laboratory of Neurochemistry
Seymour Kaufman, Ph.D.

The main effort of this laboratory is devoted to studies of the regulation of the synthesis of the biogenic amine neurotransmitters dopamine, norepinephrine, and serotonin. Current research involves the molecular characterization of the phenylalanine, tyrosine, and tryptophan hydroxylases—the enzymes that catalyze the rate-limiting steps in the biosynthesis of these neurotransmitters—as well as the enzymes involved in the biosynthesis of the coenzyme that is essential for these reactions, tetrahydrobiopterin. The researchers are studying the regulation of these enzymes by hormones, drugs, membrane depolarization, and diet, using techniques such as high pressure liquid chromatography and affinity chromatography and tools such as monoclonal antibodies. Also being investigated is the regulation of the activity of these enzymes with the aid of recombinant DNA technology and genetically engineered proteins.

Biological Psychiatry Branch
Robert M. Post, M.D.

This laboratory is engaged in studies of the clinical and behavioral pharmacology of various psychotropic drugs, particularly antidepressants, antipsychotics, anxiolytics, and anticonvulsants. The anticonvulsant carbamazepine

has recently been found to have acute and prophylactic effects in both phases of manic-depressive illness. Studies are aimed at elucidating the possible mechanisms of action of this drug in seizure and affective disorders based on studies of clinical populations and laboratory animals.

Investigators would work in a multidisciplinary laboratory environment where active interchange among clinicians and basic scientists is encouraged. The laboratory component (which could form the entire fellowship experience or be integrated with a clinical phase) could also involve studies of the behavioral pharmacology of chronic psychomotor stimulant administration and the neural mechanisms underlying long-term behavioral and physiologic changes observed in electrophysiological kindling and in learned helplessness. Techniques of clinical pharmacology, biochemistry, and behavioral analysis, with a particular focus on the roles of conditioning and learning mechanisms in long-term changes in behavior, would be emphasized. Fellows would be able to learn techniques of behavioral pharmacology, animal modeling, biochemistry, and physiology based on *in vivo* and tissue-slice preparations, and would study the biochemistry of classical neurotransmitters and peptides and their receptors using a variety of techniques, including receptor autoradiography. The fellowship would involve intensive individual work on one or more projects that would be designed, conducted, presented, and written up for publication by the fellow under the supervision and tutelage of the preceptor.

Biological Psychiatry Branch
Agu Pert, Ph.D.

This laboratory is concerned with analyzing the mechanisms of action of psychoactive drugs and neuropeptides in the brain and defining the neurochemical coding of brain circuits that control specific behaviors. Methods used include extracellular single-cell recording as well as iontophoretic techniques with drugs in specific brain regions. Lesion and microinjection procedures are then utilized to relate these effects to behavior. Current emphasis is on two projects: the actions of endorphins and enkephalins on brain function, especially the processing of pain information, and the effects of lithium (a therapeutic agent in manic-depressive illness) on neurotransmitter receptor sensitivity.

Biological Psychiatry Branch
Neurochemistry Unit
Paul J. Marangos, Ph.D.

A major research focus in this unit concerns the characterization of mechanisms involved in the action of various CNS depressants. Major attention has recently focused on the role of adenosine as a neuromodulator. Work in this laboratory has contributed to the identification of both adenosine receptors and adenosine uptake sites using specific radioligand probes. Pharmacological studies involve the mechanism of caffeine and carbamazepine action on the adenosine system, while autoradiographic studies have generated rather extensive regional maps of both the receptor and uptake sites. A major goal of the laboratory is to develop new sedative anxiolytic and antihypertensive agents that act selectively on peripheral or central adenosine sites.

A second major area of investigation within the unit relates to the neuron-specific enzyme neuron-specific enolase (NSE). This group has constructed specific cDNA probes for human brain NSE and is studying the mechanisms that mediate the synthesis of this protein. Since it has previously been shown that the synthesis of NSE is tightly coupled to neural differentiation (synaptogenesis), these studies are expected to provide key insights concerning the mechanisms of neuron-specific gene expression.

Laboratory of Cell Biology
Michael J. Brownstein, M.D., Ph.D.

The members of this group want to locate peptidergic neurons in the CNS and to characterize them anatomically. In addition, they want to learn how peptidergic neurons synthesize, transport, store, and release their biologically active products. The investigators hope to show how these processes are regulated by hormones and neurotransmitters at the transcriptional, translational, and post-translational levels. Finally, they are engaged in characterizing neurotransmitter receptors in order to determine more about the molecular basis of signal transduction.

Laboratory of Cell Biology
Section on Pharmacology
Julius Axelrod, Ph.D.

The section engages in several areas of research related to biochemical pharmacology. These include studies on

the development of methods for the measurement of hormones, biogenic amines, and enzymes; the distribution and metabolism of hormones; and the isolation and characterization of enzymes involved in hormone and biogenic amine metabolism. The laboratory also engages in examining control mechanisms of hormone and neurotransmitter secretion, methylation reactions, and signal transduction mechanisms.

Laboratory of Cell Biology
Section on Biochemical Pharmacology
Martin Zatz, M.D., Ph.D.

Current work is on problems in two areas: one concerns the mechanisms by which circadian rhythms are generated and regulated, and the other concerns the regulation of membrane metabolism by light and neurotransmitters. Related topics include brain inositide and cyclic nucleotide metabolism, vitamin A and photoreception, and the pineal gland. Biochemical and pharmacological approaches to these problems are emphasized.

Clinical Neuroscience Branch
Section on Preclinical Studies
Section on Molecular Pharmacology
Steven M. Paul, M.D.

The major research interests of the Sections on Preclinical Studies and Molecular Pharmacology involve characterizing and defining the basic neurochemical and electrophysiological mechanisms of synaptic transmission, as well as the interaction of psychotropic drugs (minor tranquilizers, antidepressants, sedatives, stimulants, and antipsychotics) with these mechanisms. Many studies involve characterization of neurotransmitter and drug receptors and recognition sites, characterization of ion channels, and definition of the relevant interactions of psychotropic drugs with these membrane proteins. Several receptor-effector systems and drug recognition sites are currently under investigation, including receptors for benzodiazepines/GABA, tricyclic antidepressants, psychomotor stimulants (amphetamine, methylphenidate), acetylcholine, serotonin, adenosine, and various neuropeptides (e.g., cholecystokinin). The role and regulation of these systems are investigated by: (1) biochemical and pharmacological characterization of the recognition sites (including purification of receptor protein using affinity chromatography), defining receptor subunits by gel electrophoresis and radiation inactivation, and the production of selective monoclonal antibodies to define functional receptor domains labeled by various radioligands; (2) isolation and characterization of the endogenous modulators of these sites using multiple chromatographic methods; (3) development of appropriate *in vitro* models for studying these receptor-effector systems (brain slices, tissue culture); (4) structure-activity studies of chemically modified substances that are related to the naturally occurring ligands; (5) behavioral and pharmacological experiments in animals (J. Crawley); (6) genetic studies in inbred strains of rats and mice, coupled with an examination of receptor-receptor-effector changes in correlation with the behavioral manifestations of these genetic mutations; (7) post-receptor events, including calcium transport, cyclic nucleotide changes, and agonist-induced phosphatidylinositol hydrolysis; and (8) electrophysiological experiments using single-unit recording techniques (L. Skirboll, D. Hommer) which are integrated with the biochemical studies in an attempt to relate these findings to physiologic changes in neuronal excitability.

Clinical Neuroscience Branch
Section on Brain Biochemistry
Candace B. Pert, Ph.D.

It has recently become apparent that neurosecretions (neurotransmitters, etc.) and many psychoactive drugs share a common site of initial action—the neuronal cell-surface receptor. This section uses radiolabeled ligands with fully preserved biologic activity to study drug and neurotransmitter receptors not only in membrane preparations, but also on thin slices of unfixed frozen brain tissue in which neuroanatomical relationships and even cytoarchitecture are fully preserved. Brain receptors and their endogenous peptide ligands can be readily mapped at the light level using computer-assisted densitometry of autoradiographic films. Opiate receptors and their ligands, the opiate peptides, remain the primary focus, with emphasis on identifying opiatergic neurocircuitry, systematic phylogenetic variation, and the biochemistry and morphologic significance of Type 1 (conformationally plastic) and Type 2 (conformationally static) opiate receptors. Other neuropeptides and their receptors (e.g., angeldustin, bombesin, substance P, neurotensin, CCK) are also being studied. In short, the thrust of the laboratory's efforts is the characterization, measurement, visualization, and solubilization of brain receptors as well as other neuronal antigens, located both on the cell surface and internally.

Laboratory of Clinical Science
Section on Clinical Pharmacology
Juan M. Saavedra, M.D.

This section's research program focuses on three areas: the central mechanisms involved in the control of pituitary function and sympathetic activity, the localization and characterization of brain neuropeptide and amine receptors by quantitative autoradiography, and the regulation of the immune system by sympathetic nerves and hormones. The scientists use a combination of microanalytical techniques, radioenzymatic assays, radioimmunoassays, and high pressure liquid chromatography to study the metabolism of biogenic amines and neuropeptides in selected brain areas of several experimental and genetic animal models. The section is also interested in the utilization and development of image analysis techniques with computerized microdensitometry for autoradiographic quantitation and characterization of receptors for neuropeptides and biogenic amines in single nuclei of rat and human brain cells.

Laboratory of Clinical Science
Section on Histopharmacology
David M. Jacobowitz, Ph.D.

A major aim of this section is to study the basis of behavioral regulation and pathologic changes by a multidisciplinary approach to CNS neurotransmitter or neurochemical systems. Histochemical, neurochemical, and physiologic analyses are carried out at the level of discrete brain regions and pathways in order to define the underlying basis for behavioral changes, drug effects, and sexual and aging differences. Drugs, stress, electrical stimulation, and surgical stereotaxic lesions are used to correlate changes in neuronal function with various parameters of behavior. Neuronal amines, peptides, proteins, and enzymes are measured within specific nuclei, tracts, and other discrete regions of the brain using a microdissection method, radioisotopic assays, and immunocytochemical methods. Two-dimensional gel electrophoresis and column chromatography are being used for the isolation and purification of brain proteins.

Laboratory of Preclinical Pharmacology
Section on Neuropeptides
Hsiu-Ying T. Yang, Ph.D.

This section is concerned with research on the neuropeptides in the brain and peripheral nervous system. Current studies are on the characterization of the enzymes involved in the metabolism of enkephalin and related peptides. Based on the characteristics of these enzymes, their inhibitors are searched for and used to aid in exploring the role of endogenous opioid peptides. The role of endogenous opioid peptides in analgesia, the mechanism of morphine tolerance, and the interaction of opiates with other neuropeptides are also being investigated.

Laboratory of Preclinical Pharmacology
Group on Immunochemistry
De-Maw Chuang, Ph.D.

This group conducts research in several areas related to molecular neuropharmacology. These include studies on: (1) molecular events of internalization of β-adrenergic receptors in cells desensitized with β-adrenergic agonists; (2) mechanisms of action of antidepressant drugs with emphasis on the physiologic and pharmacological roles of high-affinity recognition sites for these drugs; and (3) regulation by neurotransmitters and neuromodulators of phospholipid metabolism by phospholipases A2 and C in cultured tumor cells, rat aorta, and brain slices. This laboratory also uses hybridoma and cDNA techniques to quantitate neuropeptide mRNA levels.

OTHER LABORATORIES AND PRECEPTORS

NATIONAL CANCER INSTITUTE

Laboratory of Biochemistry
Dr. Maxine Singer
Protein Chemistry Section
Dr. Elbert Peterson
Biosynthesis Section
Dr. Edward Kuff
Cellular Regulation Section
Dr. O. Wesley McBride
Macromolecular Interactions Section
Dr. Claude Klee

Laboratory of Molecular Biology
Cell Organization Section
Dr. Seymour Wollman
Gene Regulation Section
Dr. B. De Crombrugghe
Ultrastructural Cytochemistry Section
Dr. Mark C. Willingham
Membrane Biochemistry Section
Dr. Kenneth Yamada
Developmental Genetics Section
Dr. Sankar L. Adhya
Molecular Genetics Section
Dr. Bruce Howard

Laboratory of Pathophysiology
Dr. Pietro M. Gullino
Cellular Biochemistry Section
Dr. Yoon S. Cho-Chung
Cell Cycle Regulation Section
Dr. W. Kidwell
Membrane Biology Section
Dr. P. Pinto Da Silva

Laboratory of Mathematical Biology
Membrane Structure and Function Section
Dr. Robert P. Blumenthal
Theoretical Immunology Section
Dr. Charles Delisi
Image Processing Section
Dr. Lewis Lipkin

Dermatology Branch
Dr. Stephen Katz

Metabolism Branch
Dr. Thomas W. Waldmann

Cellular Immunology Section
Dr. R. Michael Blaese

Laboratory of Pathology
Dr. Lance Liotta
Surgical Pathology and Postmortem Section
Dr. Ernest Lack
Cytopathology Section
Dr. Elizabeth W. Chu
Ultrastructural Pathology Section
Dr. Timothy Triche
Hematopathology Section
Dr. Elaine S. Jaffe
Biochemical Pathology Section
Dr. David A. Zopf

Immunology Branch
Dr. David Sachs
Immunotherapy Section
Dr. R. Hodes

Laboratory of Cell Biology
Dr. Lloyd W. Law
Chemistry Section
Dr. Ettore Appella

Laboratory of Genetics
Dr. Michael Potter

Laboratory of Immunobiology
Cellular Immunity Section
Dr. Berton Zbar
Humoral Immunity Section
Dr. Tibor Borsos
Immunopathology Section
Dr. Edward J. Leonard

Laboratory of Cellular Oncology
Dr. Douglas Lowy

Laboratory of Tumor Immunology and Biology
Dr. Jeffrey Schlom
Oncogenetics Section
Dr. Robert Callahan
Biochemistry of Oncogenes Section
Dr. Robert H. Bassin
Cellular and Molecular Physiology Section
Dr. Herbert Cooper

Laboratory of Molecular Virology
Dr. George Khoury
Cell Physiology Section
Dr. Gilbert Jay

Laboratory of Cellular and Molecular Biology
Dr. Stuart Aaronson
Molecular Genetics Section
Dr. E. Premkumar Reddy
Molecular Biology Section
Dr. Stuart Aaronson
In Vitro Carcinogenesis Section
Dr. Katherine Sanford-Mifflin
Gene Structure Section
Dr. Steven R. Tronick

Laboratory of Molecular Oncology
Dr. Takis Papas
Cellular Transformation Section
Dr. John Bader
Microbiology Section
Dr. Donald Blair
Molecular Control and Genetics Section
Dr. Donald L. Court

Laboratory of Viral Carcinogenesis
Dr. Stephen J. O'Brien
Cell Biology Section
Dr. Nancy Colburn
Viral Pathology Section
Dr. Ulf Rapp

Laboratory of Biology
Dr. Joseph Dipaolo
Tumor Biology Section
Dr. Charles Evans

Laboratory of Molecular Carcinogenesis
Dr. Harry V. Gelboin
Cell Genetics Section
Dr. Takeo Kakunaga
Nucleic Acid Section
Dr. Rufus Day
Protein Section
Dr. Andrew C. Peacock

Laboratory of Chemoprevention
Dr. M. Sporn

Laboratory of Cellular Carcinogenesis and Tumor Promotion
Dr. Stuart Yuspa
Differentiation Control Section
Dr. Luigi Deluca

Laboratory of Experimental Carcinogenesis
Biopolymer Chemistry Section
Dr. Peter Roller

Laboratory of Human Carcinogenesis
In Vitro Carcinogenesis Section
Dr. John Lechner
Biochemical Epidemiology Section
Dr. Dean Mann

Laboratory of Experimental Pathology
Dr. Umberto Saffiotti
Tissue Culture Section
Dr. M. Edward Kaighn

Laboratory of Comparative Carcinogenesis
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Dr. Ursula Heinee
Nutrition and Metabolism Section
Dr. Lionel Poirier
Tumor Pathology and Pathogenesis Section
Dr. Jerrold Ward
Chemistry Section
Dr. Larry Keefer

Biological Therapeutics Branch
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Immunopharmacology Section
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Clinical Investigations Section
Dr. Ronald Stein
Monoclonal Antibody/Hybridoma Section
Dr. John Pearson
Natural Immunity Section
Dr. Craig Reynolds

Laboratory of Molecular Immunoregulation
Dr. Joost Oppenheim
Lymphokines Section
Dr. Francis Ruscetti
Immunobiology Section
Dr. Luigi Varesio

Laboratory of Pharmacology and Experimental Therapeutics
Medicinal Chemistry Section
Dr. John S. Driscoll

Laboratory of Molecular Pharmacology
Dr. Kurt W. Kohn
Chromosome Structure and Function Section
Dr. William Bonner

Laboratory of Tumor Cell Biology
Dr. Robert C. Gallo
Hematopoietic Cellular Control Mechanisms Section
Dr. Robert C. Gallo
Molecular Genetics of Hematopoietic Cells Section
Dr. Flossie Wong-Staal

Pediatric Branch
Dr. Philip Pizzo
Leukemia Biology Section
Dr. David Poplack
Infectious Diseases Section
Dr. Philip Pizzo
Molecular Genetics Section
Dr. Mark Israel

Radiation Oncology Branch
Dr. Eli Glatstein
Radiation Therapy Section
Dr. Alan Zabell
Radiation Physics and Computer Automation Section
Dr. Jan Van De Geijn
Radiation Biology Section
Dr. James Mitchell
Inorganic and Radioimmune Chemistry Section
Dr. Otto Gansow

Surgery Branch
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Tumor Immunology Section
Dr. Steven Rosenberg
Surgical Metabolism Section
Dr. Jeffrey Norton
Colorectal Cancer Section
Dr. Paul Sugarbaker
Thoracic Oncology Section
Dr. Jack Roth
Urologic Oncology Section
Dr. W. Marston Linehan

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Dr. Bruce Chabner
Pharmacokinetics Section
Dr. Jerry M. Collins
Biophysical Pharmacology Section
Dr. Jack S. Cohen

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Dr. Stephen Epstein

Hypertension-Endocrine Branch
Experimental Therapeutics Section
Dr. Harry Keiser

Surgery Branch
Dr. Richard Clark

Pulmonary Branch
Dr. Ronald G. Crystal

Laboratory of Biochemistry
Dr. Earl R. Stadtman
Intermediary Metabolism and Bioenergetics Section
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Dr. Norman Salem
Section of Neurochemistry
Dr. Robert Eskay
Section of Clinical Biochemistry and Pharmacology
Dr. Elizabeth Lane

Laboratory of Metabolism
Dr. Richard L. Veech

SCHEDULE FOR APPOINTMENTS BEGINNING JULY 1, 1988 AND 1989

NOVEMBER 17, 1986: Final date for the receipt of completed application

APPLY TO: Pharmacology Research Associate Program
National Institute of General Medical Sciences
National Institutes of Health
Westwood Building, Room 919
Bethesda, Maryland 20892
Telephone: (301) 496-7707